Research Design: Background

Contents

I. Purpose and Design of this Module

The Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) conducts research and develops reports and other materials for public distribution in order to advise the President of the United States on bioethical issues that arise as a consequence of advances in biomedicine and related areas of science and technology. To support ethics

education and facilitate the integration of bioethical analysis into existing curricula across traditional and nontraditional educational and professional settings, we have developed pedagogical materials designed to increase distribution of the Bioethics Commission's work and to facilitate easy access to the material in its reports by professors, instructors, teachers, and professional leaders (collectively "instructors").

This module was prepared for instructors who want to include a discussion of ethical issues related to research design in their teaching. It provides foundational information, ethical reasoning, applications, questions, discussion points, and additional readings that are designed to give instructors enough information to plan lectures, discussions, or activities. These materials are not intended to be a lecture script or outline, but rather to support instructors in developing their own presentation(s).

In addition to the background information provided here, further modules provide a guide for instructors to facilitate incorporation of the Bioethics Commission's published reports as a resource for teaching and discussion. The featured Bioethics Commission reports illustrate relevant and current applications of ethical research design.

Instructors are invited to use these materials, or any portion of them, to integrate bioethics into coursework and professional development activities in all disciplines. Feedback is welcome, including insight into how the materials have been used and suggestions for how they might be improved for use in the future. (Send feedback to education@bioethics.gov.)

II. Introduction

Scientific research is conducted for varying purposes, including gathering preliminary information to help define a scientific problem; describing a structure or phenomenon; developing new scientific methods and tools; generating or testing a scientific theory or hypothesis; and evaluating the effectiveness of a policy or program, among others. Many methods are used for conducting scientific research, but above all, research can be considered good science only if it is conducted ethically. Moreover, researchers must "do the best science to do the best ethics."[1]

Developing a sound research design is an essential first step in conducting ethical research. Research design encompasses the entire span of a research project, from its earliest stages, when researchers review other relevant scientific theory and research findings, and formulate questions and hypotheses, to the final analyses and disposition of the data.[2] A sound research design is one

[1] Gutmann, A., Chair, Presidential Commission for the Study of Bioethical Issues (PCSBI). (2015). Ethical Issues Associated with Research in the Context of a Public Health Emergency. Remarks to PCSBI, February 5. Retrieved March 19, 2015 from http://bioethics.gov/node/4590.
[2] Boeije, H.R. (2010). *Analysis in Qualitative Research*. Thousand Oaks, CA: SAGE Publications; Parfrey, P.S., and P. Ravani. (2015). On Framing the Research Question and Choosing the Appropriate Research Design. In P.S.

that is appropriate to the research goals, addresses the practicalities of the research context, and meets relevant scientific and ethical standards and regulatory requirements. To conduct research that will not yield interpretable results is unethical—in the best case, it is a waste of limited resources; in the worst case, it subjects participants to potential harm with no possibility of furthering knowledge.

The Bioethics Commission has addressed several ethical and societal considerations that apply when designing certain kinds of research studies. For example, in *New Directions: The Ethics of Synthetic Biology and Emerging Technologies* (*New Directions*), the Bioethics Commission addressed ethical questions that arise in an emerging area of science in which risks are not yet well defined. In *Moral Science: Protecting Participants in Human Subjects Research*, the Bioethics Commission focused on complexities germane to ensuring ethical research involving human participants, such as site selection and using placebos in clinical trials. And in *Gray Matters: Integrative Approaches for Neuroscience, Ethics, and Society* (*Gray Matters*, Vol. 1), the Bioethics Commission outlined the importance of incorporating strategies to identify and address ethical and societal questions from the beginning and throughout a research endeavor.

Ethical and societal considerations arise in the design of all scientific research, whether conducted in a chemistry laboratory, in a community as part of an outbreak investigation, or in a high-technology clinical setting. This module examines key ethical and societal questions requiring consideration when designing research studies and reviews ethical principles relevant to research design. Although many kinds of research exist and all should be ethically designed, this module focuses on biomedical intervention research, a class of research addressed in several Bioethics Commission reports. It uses the example of randomized controlled trials involving human participants to demonstrate ethical considerations that can arise when designing biomedical intervention research. In addition, it provides a summary of selected relevant regulatory requirements and international guidelines.

III. Learning Objectives

After completing this activity, students should be able to:

1. Understand and discuss ethical principles that guide research design.

2. Describe methods and approaches in human subjects research that reflect best practices in ethical research design.

Parfrey and B.J. Barrett. (Eds.). *Clinical Epidemiology: Practice and Methods*, Second Edition (pp. 3-18). New York, NY: Humana Press; USC Libraries. (2015). Organizing Your Social Sciences Research Paper: Types of Research Designs [Webpage]. Retrieved March 20, 2015 from http://libguides.usc.edu/c.php?g=235034&p=1559832.

3. Identify how existing regulations and guidelines address considerations of research design.

IV. Background

A. Ethical Considerations

A sound research design considers overarching goals and tenets common to most scientific research, the specific objectives of the research project, standards of the relevant scientific discipline or disciplines, and ethical principles that guide scientific research. Several principles underlie the requirements for ethical research design in human subjects research, three of which are described in the *Belmont Report*, authored by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) in 1978 to serve as a guide for ethical human subjects research.[3] These include respect for persons, beneficence, and justice.

The Bioethics Commission has articulated additional relevant principles, which include public beneficence, responsible stewardship, and democratic deliberation.[4]

Respect for Persons

Respect for persons establishes that all individuals (in this case, research participants) should be respected as autonomous decision makers. Autonomy refers to the ability of an individual to understand information, deliberate about personal goals, and make decisions freely, and is at the heart of informed consent.[5] Respect for persons demands that a robust informed consent process be part of all research protocols involving human participants. Individuals with diminished capacity to give informed consent are entitled to additional protection (although some scholars view additional protections as a matter of beneficence, rather than respect for persons).[6] In addition, studies designed to achieve valid and meaningful results justify the risks to which participants are exposed and respect their time and effort.[7]

[3] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission). (1978). *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (DHEW Publication OS 78-0012). Washington, DC: Department of Health, Education, and Welfare. Retrieved March 19, 2015 from http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html.
[4] PCSBI. (2010, December). *New Directions: The Ethics of Synthetic Biology and Emerging Technologies.* Washington, DC: PCSBI.
[5] National Commission, op cit.
[6] Ibid.
[7] Moreno, J.D. (1999). Ethics of research design. *Accountability in Research*, 7, 175-182; PCSBI. (2011, December). *Moral Science: Protecting Participants in Human Subjects Research*. Washington, DC: PCSBI, p. 93.

Beneficence

In human subjects research, the principle of beneficence obligates the researcher to act in a way that secures the wellbeing of research participants. A corollary to the principle of beneficence is non-maleficence, which requires the researcher not to impose harm and to minimize harm that might occur to participants, for example, as a result of poor research design that unnecessarily exposes participants to risk.[8] Sound research design is crucial to ensuring that research participants are protected from avoidable harm and unethical treatment.

Public Beneficence

The principle of public beneficence encourages researchers to pursue and secure public benefits while minimizing personal and public harm. The concept of public beneficence applies both to research with human participants and research that does not involve human participants but still has broader implications for society. Investigators should be mindful of the risks and benefits of their research more broadly, designing studies to maximize the likelihood that results will advance scientific knowledge and public benefit while minimizing potential risks to society and the environment.[9]

Justice

The principle of justice calls for equitable distribution of benefits and burdens across society. It requires that a project's research design not place undue burden on any specific group without compensating benefits.[10] That is, the potential benefits and risks of research should be distributed equitably. For example, fair participant selection and site selection can ensure that researchers do not offer potentially beneficial research only to a group of favored individuals, or that risky research is not borne by a specific population.[11] Injustice can occur when benefits of research accrue only to some or when some individuals or groups bear an unequal burden of research-related risks. The principle of justice is particularly relevant when research is conducted among populations who might be vulnerable to coercion or discrimination.[12]

Responsible Stewardship

The principle of responsible stewardship calls for researchers to ensure and promote consideration of the interests and needs of those not in a position to represent themselves in

[8] National Commission, op cit.
[9] Moreno, J.D., op cit; PCSBI, (2010, December), op cit.
[10] National Commission, op cit; Moreno, J.D., op cit.
[11] National Commission, op cit.
[12] Marshall, P.A. (2007). *Ethical Challenges in Study Design and Informed Consent for Health Research in Resource-Poor Settings.* Geneva, Switzerland: World Health Organization. Retrieved March 20, 2015 from http://whqlibdoc.who.int/publications/2007/9789241563383_eng.pdf?ua=1.

social discourse.[13] It requires that investigators be mindful of and attentive to potential risks as they develop, plan, and conduct their research. Scientists have a duty to be accountable stewards of resources dedicated to research and to conduct science responsibly. Responsible stewards exhibit prudent vigilance and establish processes for assessing likely benefits and risks at all stages of the research process and as technologies diffuse into public and private sectors.[14]

Scholars also endorse that responsible stewardship involves choosing a research topic that can provide information useful to society. Information gained from research should be published promptly and in a way that avoids undue repetition of experiments while ensuring that confirmation of previous findings are available to the scientific community. Finally, scholars advocate that responsible stewardship includes identifying ethical quandaries in one's work and helping to address or resolve ethical problems.[15]

Democratic Deliberation

The principle of democratic deliberation reflects an approach to collaborative decision making that seeks to clarify and articulate factual and ethical questions at the core of a debate, to create consensus whenever possible, and to map the terrain of disagreements in a respectful way—when agreement is not immediately attainable—by encouraging reciprocity, respect for persons, transparency, public scrutiny, and accountability.[16] Democratic deliberation can constitute an important step early in the research design process as researchers seek to engage diverse input before research begins. An open discussion and debate can promote the legitimacy of outcomes and an atmosphere of mutual respect, even if outcomes do not satisfy all interested parties and differences cannot be reconciled.[17]

B. Ethical Study Design

Ethical study design requires careful consideration of the previously described principles. This section focuses on ethical research design generally and discusses randomized controlled trials involving human participants specifically—a type of research in which the ethical considerations that can arise serve as examples applicable to many other research contexts.

Research design is the general plan for testing a specific hypothesis and obtaining results. A primary ethical consideration of research design is its scientific merit. Ethical research design also must be scientifically sound. It would be unethical to subject participants to risk, inconvenience, or discomfort if the research design is flawed and cannot yield valid results.

[13] PCSBI, (2010, December), op cit, pp. 4, 123.
[14] Ibid.
[15] Bulger, R.E. (2002). The Responsible Conduct of Biological and Health Research. In R.E. Bulger, E. Heitman, and S.J. Reiser (Eds.). *The Ethical Dimensions of the Biological and Health Sciences,* Second ed. (pp. 57-63). Cambridge, UK: Cambridge University Press, p. 61.
[16] PCSBI, (2010, December), op cit, pp. 5, 151.
[17] Ibid.

Researchers often can choose from several options when designing a study to test a hypothesis, each with its own advantages and disadvantages. An ideal plan might not exist for answering a research question, but researchers must select a design that will yield valid and interpretable results and consider that design in light of available resources, such as time and money.[18] Researchers must consider not only what is the most scientifically sound research design to answer a research question, but also what is the most ethical approach.

Categories of Research Design

Different research designs achieve different goals. Most research designs fall into two categories: experimental (also called *interventional*) and observational (also called *descriptive* or *correlational*). Experimental studies test the effect of a treatment or procedure on a specified outcome measure. For example, an experiment might test whether a particular drug is successful at reducing appetite among overweight adults. In this case, the drug is the study intervention. The reduction in appetite is the outcome to be measured. True experimental designs have the elements of manipulation (the ability to manipulate one variable), control (the ability to prevent outside factors from influencing the study outcome), and randomization (the random, unbiased selection and assignment of the research sample). Quasi-experimental designs exist and are used in specific circumstances when randomized controlled trials are methodologically or ethically inappropriate.[19]

If researchers conclude that an experimental design is inappropriate or unfeasible, they might choose to conduct an observational study. Observational studies do not manipulate the research environment but instead seek to collect and report information. For example, researchers might observe the eating habits of overweight adults. Observational studies also can be conducted to demonstrate associations in real-world scenarios, such as studying medical histories to determine whether smoking is associated with obesity. However, observational studies often lack the element of control, leading to a greater potential for biases.[20]

Although scientific merit is required for a study design to be ethical, not all scientifically sound research designs are necessarily ethically appropriate. As described in the Bioethics Commission report *"Ethically Impossible": STD Research in Guatemala from 1946 to 1948*, controlled experiments conducted in Guatemala and supported by the United States involved infecting human research participants with sexually transmitted microbes without the participants'

[18] Panacek, E.A., and C.B. Thompson. (1995). Basics of research (Part 3): Research study design. *Air Medical Journal*, 14(3), 139-146; Office of Research Integrity (ORI). (n.d.). Research Design [Webpage]. Retrieved March 20, 2015 from http://ori.hhs.gov/education/products/sdsu/res_design.htm.
[19] Panacek, E.A., and C.B. Thompson, op cit.
[20] Panacek, E.A., and C.B. Thompson, op cit; ORI, op cit.

consent.[21] In this example, controlled trials were ethically inappropriate and highlight the need to incorporate ethical considerations into research design planning.

Research Risk

When selecting a research design for human subjects research that involves an experimental intervention, researchers must consider the ethics of interventional research, including risk assessment. Federal regulations define interventions as "both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes."[22] The ethical principles of human subjects research require that researchers avoid exploitation of research participants; moreover, anticipated risks must be reasonable with respect to anticipated benefits. However, anticipated benefits might include the social value of experimental results, with no prospect of direct benefit to individual participants. To determine whether anticipated benefits (to society as a whole or to the individual participant) outweigh potential risks, proposed research first must undergo an assessment of the risks of the intervention. A risk assessment ensures sufficient justification exists to include the intervention in the study in question, attempts to enhance the benefits and minimize the risks of the intervention, and assesses the acceptability of the risks of the intervention. Although U.S. federal regulations do not mandate limits of acceptable risk for competent adults, limits exist regarding the level of acceptable research risks for individuals who are unable to provide their own informed consent.[23]

Sample Size

Research design also includes decisions about the size of the sample to be studied. In human subjects research, *sample size* refers to the number of participants in the study. An appropriate sample size is large enough to detect a true difference between studied groups among a population and provides reasonable assurance that no difference exists if it is not found during the investigation.[24] Researchers can use different methods for determining a suitable sample and size, and researchers should select the method most likely to yield valid results.[25]

Researchers also must consider the ethical aspects of sample size determination. A sample size that is too small might not be sufficient to differentiate the observed effect size from chance and might not yield valid results. As a consequence, a sample size that is too small would

[21] PCSBI. (2011, September). "*Ethically Impossible": STD Research in Guatemala from 1946 to 1948*. Washington, DC: PCSBI.
[22] *Protection of Human Subjects, Department of Health and Human Services (HHS)*. 45 C.F.R. § 46.102(f).
[23] Wendler, D., and F.G. Miller. (2008). Risk-Benefit Analysis and the Net Risks Test. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 503-513). New York, NY: Oxford University Press, pp. 503-504; Wendler, D. (2012). The Ethics of Clinical Research. In E.N. Zalta. (Ed.). *The Stanford Encyclopedia of Philosophy*. Retrieved March 11, 2015 from http://plato.stanford.edu/entries/clinical-research/.
[24] Altman, D.G. (1991). *Practical Statistics for Medical Research*. New York, NY: Chapman & Hall, p. 455.
[25] Thompson, C.B., Panacek, E.A., and E. Davis. (1995). Basics of research (Part 4): Research study design (Part 2). *Air Medical Journal*, 14(4), 222-231.

unnecessarily expose participants to risk and would be unethical. In contrast, a sample size that is too large would expose more participants than necessary to research risks and would be a waste of resources.[26] The clinical research enterprise addressed the tension between exposing too many participants to research risk and the need for a sufficient sample size by implementing a system in which a small sample is used in the early testing of an experimental treatment and increasing the sample size as more is learned about the treatment's safety profile.[27]

Data Collection and Analysis

Researchers also consider during the planning phase how data will be collected, measured, and analyzed. Researchers have several data collection methods from which to choose and can select the appropriate method on the basis of the research question and design.[28] Identifying which statistical method to use to analyze data at the outset allows researchers to specify the questions that can be answered with the data and prevents collection of data that would not address the study question.[29] Researchers should be aware of the limitations of their chosen data collection methods and take steps to maximize the validity of measurements and data-collection instruments.[30]

Sharing Results

Researchers have an obligation to each other and to society to publish results, so that others can benefit and science can progress. Ethical norms in research, including guidelines for authorship, copyright, and patenting policies; data sharing policies; and confidentiality rules in peer review, encourage collaboration and sharing of results while protecting individual researchers' interests.[31] Consequences of failing to share results or publishing substandard research include unnecessarily exposing research participants to the risks and inconveniences of research, misusing resources, and failing to guide (or misguiding) future research and treatment paradigms.[32] The researcher's obligation to share results extends to the sharing of negative results. Not sharing negative results would be unethical, especially if participants were exposed

[26] Devane, D., Begley, C.M., and M. Clarke. (2004). How many do I need? Basic principles of sample size estimation. *Journal of Advanced Nursing*, 47(3), 297-302, p. 298.
[27] Clinical research is conducted in a series of steps, called phases. As an experimental intervention progresses through the clinical trial phases, it is tested on an increasingly larger sample of research participants. Wendler, D. (2012), op cit.
[28] Thompson, C.B., Panacek, E.A., and E. Davis, op cit.
[29] Myers, J.L., Well, A., and R.F. Lorch. (2010). *Research Design and Statistical Analysis: Third Edition*. New York, NY: Routledge, p. 4.
[30] Thompson, C.B., Panacek, E.A., and E. Davis, op cit.
[31] Resnik, D.B. (2011). What is ethics in research & why is it important? [Webpage]. National Institute of Environmental Health Sciences. Retrieved March 20, 2015 from http://www.niehs.nih.gov/research/resources/bioethics/whatis/; National Institutes of Health (NIH). (2015). Principles and Guidelines for Reporting Preclinical Research [Webpage]. Retrieved April 23, 2015 from http://www.nih.gov/about/reporting-preclinical-research.htm; McNutt, M. (2014). Journals unite for reproducibility. *Science*, 346(6210), 679.
[32] Altman, D.G., op cit, pp. 477-478, 491-492.

to risk and inconvenience with the understanding that the study would contribute to the body of scientific knowledge. Negative results contain valuable information and should become part of the scientific record to support future hypotheses and study design.[33]

Validity and Related Concepts

Validity refers to the degree to which a study (or research procedures within it) measures what it was intended or claims to measure. A result is valid if it is accurate and reflects reality.[34] Validity is often intertwined with other foundational goals of sound scientific research design. For example, it is closely associated with reliability, or reproducibility, which is the ability to replicate results.[35] Another broad goal of scientific research is generalizability, which refers to the degree to which findings can be extrapolated beyond the individual or group being studied.[36] Designing research that, to the extent possible, mitigates bias is another important dimension of scientific research design. For example, inaccurate or incomplete recall by research participants in response to interview questions about past events (*recall bias*) or the tendency to include data that support a hypothesis while excluding those that negate it (*experimenter bias*) can alter results.[37]

Researchers have a fundamental obligation to plan, design, and conduct studies with honesty, truthfulness, and integrity—values demonstrated by how researchers observe, record, and interpret their work.[38] Investigators can use a variety of experimental methods and considerations in research design to ensure that they conduct their work in a scientifically valid and ethically responsible manner. These methods include repeating experiments, using concurrent controls in

[33] Sandercock, P. (2013). Negative results: Why do they need to be published? *International Journal of Stroke*, 7(1), 32-33; Matosin, N., et al. (2014). Negativity towards negative results: A discussion of the disconnect between scientific worth and scientific culture. *Disease Models & Mechanisms*, 7(2), 171-173.
[34] Winter, G. (2000). A comparative discussion of the notion of 'validity' in qualitative and quantitative research. *The Qualitative Report*, 4(3&4). Retrieved March 20, 2015 from http://www.nova.edu/ssss/QR/QR4-3/winter.html; Trochim, W.M.K. (2006). Research Methods Knowledge Base: Reliability & Validity [Webpage]. Retrieved March 20, 2015 from http://www.socialresearchmethods.net/kb/relandval.php.
[35] Fang, F.C., and A. Casadevall. (2010). Reproducible science. *Infection and Immunity*, 78(12), 4972-4975; Creswell, J.W. (2003). *Research Design: Qualitative, Quantitative, and Mixed Method Approaches*, Second Editions. Thousand Oaks, CA: Sage Publications, p. 8; NIH. (2015). Rigor and Reproducibility [Webpage]. Retrieved April 23, 2015 from http://www.nih.gov/science/reproducibility/index.htm; McNutt, M., op cit.
[36] Tobin, G.A., and C.M. Begley. (2004). Methodological rigour within a qualitative framework. *Methodological Issues in Nursing Research*, 48(4), 388-396; Schonfield, J.W. (2002). Increasing the Generalizability of Qualitative Research. In A.M. Huberman and M.B. Miles (Eds.). *The Qualitative Researcher's Companion* (pp. 171-172). Thousand Oaks, CA: Sage Publications.
[37] Choi, B.C.K., and A.W.P. Pak. (2005). A catalog of biases in questionnaires. *Preventing Chronic Disease*, 2(1), A13; McCambridge, J., Kypri, K., and D. Elbourne. (2014). Research participation effects: A skeleton in the methodological cupboard. *Journal of Clinical Epidemiology*, 67(8), 845-849; Macleod, M.R., et al. (2009). Good laboratory practice: Preventing introduction of bias at the bench. *Stroke*, 40(3), e50-e52; Barber, T.X., and M.J. Silver. (1968). Fact, fiction, and the experimenter bias effect. *Psychological Bulletin*, 70(6, pt. 2). 1-29.
[38] Bulger, R.E., op cit, p. 59.

experiments to rule out confounding factors, and subjecting data to appropriate statistical analysis, among others.[39]

Finally, researchers meet accepted professional standards by adhering to relevant codes and regulations and practicing responsible conduct of research (discussed later in this module).

1. Design Components in Research

The inherent uncertainty in scientific research underscores the need to design research that builds on prior knowledge and minimizes potential harms. Scientific research involves an investment of time and resources to answer questions or discover new knowledge, without a guarantee of positive findings. Research can pose risks to humans, other living things, or the environment because the consequences of exploratory activities are largely unknown. For example, in the context of a new technology, such as synthetic biology, environmental and human health risks hypothetically could arise from the adverse effects of intentional or inadvertent release into the environment of engineered organisms, such as photosynthetic algae created to produce biofuels.[40]

Ethical research designs include steps for considering potential risks before the research begins as well as measures built in for assessing risks as the research advances and more information becomes available. Precautions are essential for protecting participants and the public from harm and for assuring the public that research will proceed with attention to ethical concerns and societal implications. These steps are consistent with the ethical principles of public beneficence and responsible stewardship. Potential research risks can be minimized by assessing risk levels early in the research process, monitoring research as it proceeds, building in controls to stop or slow the progression of research (or the proliferation of a dangerous agent) when ethically necessary, and staging research so that risks can be assessed and cautionary measures reevaluated as more is learned.[41] Risks also can be managed by engaging with communities to determine what levels of uncertainty they are willing to tolerate in light of the potential benefits that might result.

Integrating ethics and scientific research early and explicitly throughout the research process enables ethical research design. For example, in *Gray Matters*, Vol. 1, the Bioethics Commission emphasized how incorporating ethical perspectives at different stages of a research project can strengthen both the study itself and translation of the findings for the broader public.[42] In all areas of scientific research, individual scientists face ethical decisions when they choose research

[39] Ibid.
[40] PCSBI, (2010, December), op cit.
[41] Ibid.
[42] PCSBI. (2014, May). *Gray Matters: Integrative Approaches for Neuroscience, Ethics, and Society.* Washington, DC: PCSBI, pp. 10-11.

topics, seek funding, design and conduct research, and disseminate results, even when research does not directly involve human participants.

2. Human Subjects Research Example: Randomized Controlled Trials in Biomedical Research

As with all scientific research, human subjects research should incorporate a strong scientific rationale and methods that meet the scientific standards of the relevant discipline or disciplines. Research with human participants is necessary to advance many scientific fields. For example, many federal agencies, including the U.S. Department of Health and Human Services (HHS), U.S. Department of Transportation, U.S. Department of Energy, and the U.S. Department of Agriculture, support research involving human participants.[43] Human subjects research can involve many different types of study design and approaches from the biological, biomedical, behavioral, and social sciences. These include assessing the effects of a behavioral or clinical intervention or manipulation; reviewing, abstracting, and analyzing existing paper or electronic records or biological samples from individuals or groups; and observing or interviewing individuals or groups of people in field or laboratory settings, among others.

Randomized controlled trials (RCTs) are one category of experimental study involving human participants. RCTs are a prominent type of experimental study, in large part because they are considered the most reliable study design for assessing whether an intervention causes, rather than has a simple correlation with, the outcome of interest.[44]

RCTs are widely considered to be the ultimate scientific standard of evidence for the safety and efficacy of experimental interventions.[45] RCTs are characterized by a high level of control over the experimental conditions under which the study occurs. This control allows for research designs that increase confidence that the study is evaluating the effects of the experimental intervention rather than of other factors. However, when designing RCTs, researchers should attempt to ensure that the study's internal validity (the degree to which the outcome can be attributed to the intervention) results in external validity (the generalizability of the findings outside an artificial, experimental environment).[46]

The U.S. Food and Drug Administration (FDA) categorizes clinical trials for drugs and devices into Phases 0 through 4 on the basis of the trial's stage during the development process. Phase 0 studies are for exploratory early research, involve a limited number of participants, and do not assess therapeutic or diagnostic outcomes. Phase 1 trials also involve few participants and are

[43] See PCSBI, (2011, December), op cit, pp. 140-162; PCSBI. (n.d.). Human Subjects Research Landscape Project – Analysis Dataset [Webpage]. Retrieved March 31, 2015 from http://bioethics.gov/node/756.
[44] Besen, J., and S.D. Gan. (2014). A critical evaluation of clinical research study designs. *Journal of Investigative Dermatology*, 134, e18.
[45] Lu, C.Y. (2009). Observational studies: A review of study designs, challenges and strategies to reduce confounding. *The International Journal of Clinical Practice*, 63(5), 691-697.
[46] Thompson, C.B., Panacek, E.A., and E. Davis, op cit.

designed to assess the safety, dosage, and side effects of interventions. Phase 2 trials involve a larger group of participants, are designed to further assess safety, and sometimes efficacy or effectiveness. Phase 3 trials involve large groups of participants and evaluate efficacy or effectiveness as a primary outcome, as well as safety. Phase 4 studies collect post-marketing safety and effectiveness data after an intervention is approved and in use.[47]

Investigators consider multiple factors when designing RCTs, including the number of study groups, whether a placebo group will be included, how to select participants, and how to select a site, or several sites, for the research.

a. Key Design Features of Randomized Controlled Trials

In an RCT, research participants are assigned randomly to one of two or more groups. In the simplest RCT, two groups are included. Each group (often called a *study arm*) is characterized by an experimental condition—one group will receive an experimental intervention, and another group might receive a placebo (something that has all of the characteristics of the intervention without the active part or ingredient that the study is testing). The most familiar example of a placebo is an imitation pill in a study evaluating whether a new drug is safe or effective. One group is administered the drug with the active ingredient and the other group, an imitation pill that looks, tastes, and feels like the pill administered to the other group, but without the active ingredient. The purpose of the different arms is to compare what happens in carefully selected groups of participants who are and are not receiving the intervention.

The placebo and interventions appear as identical as possible to minimize the influence of bias associated with perceptions of intervention effects. For these reasons, participants, researchers, or others directly and indirectly involved in the trial are *blinded* to the intervention conditions (i.e., they are unaware which participants are assigned to each group). In a participant-blinded study, the participants are blinded to the intervention conditions, but the researchers involved are aware to which study arm participants are assigned. In a double-blinded study, both the participants and the researchers involved in collecting and analyzing data are unaware of the study arm assignments, further reducing the influence of bias.[48]

Not all RCTs use a placebo arm. For example, an equivalence or noninferiority trial compares the effects of an experimental intervention to an established one, which is called an *active*

[47] U.S. Food and Drug Administration (FDA). (2014). The FDA's drug review process: Ensuring drugs are safe and effective [Webpage]. Retrieved March 20, 2015 from http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm; U.S. National Library of Medicine. (2008). Clinical Trial Phases. Question: What Are Clinical Trial Phases [Webpage]. Retrieved March 20, 2015 from http://www.nlm.nih.gov/services/ctphases.html; Fromer, M.J. (2006). FDA introduces new phase 0 for clinical trials: Some enthusiastic, some skeptical. *Oncology Times*, 28(15), 18-19; FDA Center for Drug Evaluation and Research. (2006). Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies. Retrieved March 20, 2015 from http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078933.pdf.
[48] Day, S.J., and D.G. Altman. (2000). Blinding in clinical trials and other studies. *BMJ*, 321(7259), 504.

control.[49] As with all research designs, these different kinds of RCTs have scientific, logistical, and ethical advantages and disadvantages. The choice of which design to use depends on many factors.

Some scholars object to the use of a placebo arm on ethical grounds when proven treatments exist. They contend that withholding proven beneficial treatments from research participants is ethically unacceptable.[50] In addition, participants might not fully understand that they could be randomized to a placebo arm. Clinical research participants often confuse research with medical care, assuming they will not receive a placebo because the investigator—who might also be a physician—will act in their best interest. This is known as the *therapeutic misconception*.[51] The Council for International Organizations of Medical Sciences (CIOMS) guidelines, which advise restricting use of placebos in certain circumstances, address this confusion by stating that informed consent for controlled trials should include "an explanation of features of the research design (e.g., randomization, double-blinding), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken."[52]

Designing an RCT with a placebo control arm is considered to be ethically justifiable if the scientific and medical communities are genuinely unsure whether the drug or intervention being tested is more beneficial than other approved treatments or no treatment at all. This state of uncertainty is called *clinical equipoise*.[53] The presence or absence of equipoise can, in some instances, be a matter of legitimate scientific debate, particularly with novel technologies.[54] It might be caused by contradictory study results, questions about the scientific rigor of relevant evidence, or evidence from well-designed studies demonstrating moderate effectiveness or safety concerns that might be sufficient to preclude its use. In addition, some scholars disagree about whether true equipoise ever exists, because preclinical studies often suggest that the proposed experimental intervention has a chance of being effective.[55] Drug companies would be unlikely to invest in studies if that were not the case, and the FDA would not permit studies to progress to

[49] Snapinn, S.M. (2000). Noninferiority trials. *Current Controlled Trials in Cardiovascular Medicine*, 1(1), 19-21.
[50] Rothman, K.J., and K.B. Michels. (1994). The continuing unethical use of placebo controls. *The New England Journal of Medicine*, 331(6), 394-398; Moreno, J.D., op cit.
[51] Appelbaum, P.S., Roth, L.H., and C. Lidz. (1982). The therapeutic misconception: Informed consent in psychiatric research. *International Journal of Law and Psychiatry*, 5(3-4), 319-329; Appelbaum, P.S. (2002). Clarifying the ethics of clinical research: A path toward avoiding the therapeutic misconception. *The American Journal of Bioethics*, 2(2), 22-23; Miller, F.G., and H. Brody. (2003). A critique of clinical equipoise: Therapeutic misconception in the ethics of clinical trials. *Hastings Center Report*, 33(3), 19-28.
[52] The Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO). (2002). International Ethical Guidelines for Biomedical Research Involving Human Subjects. WHO. Retrieved March 20, 2015 from http://www.cioms.ch/publications/guidelines/guidelines_nov_2002_blurb.htm.
[53] Freedman, B. (1987). Equipoise and the ethics of clinical research. *The New England Journal of Medicine*, 317(3), 141-145.
[54] Freedman, B., op cit; Miller, F.G., and H. Brody, op cit.
[55] Lilford, R.J. (2003). Ethics of clinical trials from a Bayesian and decision analytic perspective: Whose equipoise is it anyway? *BMJ*, 326(7396), 980-981.

additional trials if the preliminary evidence was not encouraging. These concerns have raised some doubts about the usefulness of the concept of equipoise for justifying an RCT.[56]

Independent Data Safety Monitoring Boards (DSMBs) or Clinical Trial Data Monitoring Committees (DMCs), which periodically review study data to determine whether the study meets the standards of equipoise on the basis of new information emerging from the research, can guard against the uneven accumulation of benefits or harms to one study arm. For example, if the group receiving the experimental intervention appears to be doing substantially better in relation to certain outcomes of interest than the control group, then a DSMB might recommend that researchers discontinue the control arm and give all trial participants the experimental intervention. Conversely, if participants in a study arm are experiencing substantial adverse events or the trial is unlikely to be able to evaluate the hypothesis under study (e.g., if some participants withdraw from the trial or are lost at follow-up), the DSMB might recommend halting the study altogether.

Investigators should anticipate outcomes that can be assessed as the research progresses to help measure the safety and efficacy of each study arm.

b. Participant Selection

An important dimension of the *control* exercised in controlled trials relates to how participants are selected for study participation. Inclusion and exclusion criteria might include sociodemographic, physical and clinical characteristics, health status, and other relevant attributes. Researchers must reconcile competing priorities in defining their inclusion and exclusion criteria, including scientific rigor and feasibility, as well as justice, beneficence, and other ethical considerations. Appropriate inclusion and exclusion criteria serve to minimize bias and ensure the study evaluates what it intends to measure. They also ensure that potential research participants make an informed choice to participate in a study, and that, as a group, they are sufficiently representative of the population for which the intervention is intended.[57]

Importantly, investigators designing research should ensure that exclusion of specific groups is done for scientific reasons only. Investigators must also ensure that inclusion is not the result of coercive participation inducements (e.g., participants might be willing to take on high risk for compensation because of poverty or lack of legal protections). Moreover, investigators must consider how research might exacerbate vulnerability, even if inclusion of certain vulnerable groups is scientifically or ethically necessary.[58]

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[56] Miller, F.G., and S. Joffe. (2011). Equipoise and the dilemma of randomized clinical trials. *The New England Journal of Medicine*, 364(5), 476-480; Miller, F.G., and H. Brody, op cit.
[57] Thompson, C.B., Panacek, E.A., and E. Davis, op cit.
[58] See the *Vulnerable Populations Background* module for a further discussion of vulnerability in the research setting. The module is available at http://www.bioethics.gov/education.

In 2001, the National Bioethics Advisory Commission wrote the following in response to concerns about research with vulnerable groups and the need for ethical research design:

> The response, whenever possible, should not be to exclude people from research, but instead to change the research design so that it does not create situations in which people are unnecessarily harmed. To do otherwise is to risk developing knowledge that helps only a subset of the population. To the extent that the results are not generalizable, the potential societal benefits that justify doing the research are attenuated. Research participants must be treated equally and with respect. Whenever possible, research should be designed to encourage the participation of all groups while protecting their rights and welfare.[59]

c. Site Selection

Researchers must consider the ethical dimensions of selecting a research site. Ethical site selection involves choosing a site that allows for the protection and ethical treatment of participants and it demands that selection of a specific site does not unfairly advantage or disadvantage any particular group. Even when a clinical trial uses a scientifically sound research design and addresses important research questions, it still can be considered unethical if investigators do not choose an appropriate site for conducting the research. What might be an ethically acceptable design in one setting might not be so in another. For example, it might be unethical to conduct research on a condition in a country where that condition is unlikely to be found, simply because it is less expensive or individuals of that country are more likely to accept the risks of the research because of limited access to health care. However, the same study might be conducted ethically if it is responsive to the health needs and priorities of the local community and the results have potential for benefiting the local population.[60]

C. Relevant Regulatory Requirements and Guidelines

1. International Codes and Guidelines

International codes, such as the Nuremberg Code and the Declaration of Helsinki, provide guidelines for ethical research with human participants.[61] They require that the research be based on knowledge of the natural history of the disease and, if relevant, on animal studies; the study

[59] National Bioethics Advisory Commission (NBAC). (2001). *Ethical and Policy Issues in Research Involving Human Participants*, Summary. Bethesda, MD: NBAC, p. 4. [Emphasis removed].
[60] See PCSBI, (2011, December), op cit, pp. 82-88; NBAC, op cit.
[61] See the *Informed Consent Background* for more information about the Nuremberg Code and the Declaration of Helsinki. The module is available at http://www.bioethics.gov/education.

design conform to generally accepted scientific principles; and the research be based on the investigator's in-depth knowledge of what has already been studied and published.[62]

The internationally recognized principles of Good Clinical Research Practice (GCP) help ensure the ethical design, conduct, recording, and reporting of clinical research with human participants and are consistent with the principles enunciated in such ethical guidelines as the Declaration of Helsinki. The principles of GCP demand that clinical research designs assess the potential benefits and risks of research, incorporate a robust informed consent process, include review by an independent ethics committee, and protect the confidentiality and privacy of participants, among other considerations.[63]

2. U.S. Codes and Regulations

a. Responsible Conduct of Research

In 1989, HHS established the Office of Scientific Integrity and the Office of Scientific Integrity Review in response to the Health Research Extension Act, which required the Secretary of HHS to issue a regulation requiring institutions to establish processes for reviewing accusations of scientific fraud. In 1992, the Office of Research Integrity (ORI) was established and assumed the responsibilities of the previous offices. In addition to responding to scientific misconduct, ORI undertook steps to promote integrity and responsible research practices, including responsible conduct of research (RCR) training programs.[64]

RCR is a dimension of professional ethics and an extension of good citizenship applied to professional life. Although no universal best way to design and undertake research exists, all research should be planned and conducted responsibly and according to basic standards of a particular field, with attention to shared values, including honesty, accuracy, efficiency, and objectivity. These considerations are particularly salient when the research is publicly funded because it is crucial to maintaining the public's trust. RCR guidance varies across contexts—some practices are defined through law, whereas others are contained in nonbinding guidelines. Four sources of RCR guidance are professional codes, government regulations, institutional policies, and personal and professional values. Of note, research institutions are required by law

[62] See NIH. (n.d.). The Nuremberg Code. Retrieved March 20, 2015 from http://history.nih.gov/research/downloads/nuremberg.pdf; World Medical Association. (2013). Declaration of Helsinki [Webpage]. Retrieved March 20, 2015 from http://www.wma.net/en/30publications/10policies/b3/.
[63] WHO. (2002). Handbook for Good Clinical Research Practice (GCP): Guidance for Implementation. Retrieved March 20, 2015 from http://apps.who.int/prequal/info_general/documents/GCP/gcp1.pdf.
[64] ORI. (2011). Historical Background [Webpage]. Retrieved March 20, 2015 from http://ori.hhs.gov/historical-background; ORI. (2012). About ORI [Webpage]. Retrieved March 20, 2015 from http://ori.dhhs.gov/about-ori.

to have policies that cover certain aspects of RCR as a condition of federal funding, and research misconduct can result in loss of funding or debarment from receiving future federal funds.[65]

Research Misconduct

"*Research misconduct* means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

(a) *Fabrication* is making up data or results and recording or reporting them.

(b) *Falsification* is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.

(c) *Plagiarism* is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.

(d) *Research misconduct* does not include honest error or differences of opinion."

Source: Office of Research Integrity, Department of Health and Human Services. (2011). Definition of Research Misconduct [Webpage]. Retrieved November 10, 2014 from http://ori.dhhs.gov/definition-misconduct.

b. Protection of Human Research Participants

With respect to the ethical treatment of research participants, federal regulations have been codified by HHS in the *Code of Federal Regulations* at 45 C.F.R. Part 46 (Subpart A, which is often referred to as the "Common Rule"). These regulations require that institutional review boards (IRBs) determine that a research design appropriately minimizes risks so that "risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."[66]

Although federal regulations do not require external review bodies, such as an IRB, to assess the scientific merits of a research design, research with scientifically unsound methods will neither generate valid and reliable data nor produce generalizable and beneficial knowledge. In such cases, research participants incur the risks, inconveniences, harms, or discomforts that might occur in research without generating valid data or generalizable knowledge. Because putting individuals at risk or inconveniencing or discomforting them through participation in a flawed

[65] Steneck, N.H. (2007). *ORI: Introduction to the Responsible Conduct of Research*. Washington, DC: Department of Health and Human Services.
[66] *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.111(a)(2).

study would be unethical, the scientific merit of research is an ethical consideration, and many IRBs focus on how study designs might affect the rights and welfare of participants.[67]

V. Discussion Questions

The following questions are based on the information provided in the "Background" section above and are intended to reinforce important aspects of ethical research design and regulations and guidelines that govern such activities. Important points are noted with each question to help the instructor guide group discussions. The "Additional Resources" section will be helpful in answering these questions.

1. **Research can carry a high degree of uncertainty, especially if few prior data are available to inform us about potential benefits and risks. What elements of research design can address this level of uncertainty?**

   Starting points for discussion:

   a. The research must have a clear scientific objective with an expectation of benefit, including advancing scientific knowledge, to justify potential risks.

   b. The research must be conducted by using accepted and valid experimental practices to protect the safety of researchers, participants (if applicable), and the public (e.g., plans for containment or monitoring).

   c. The research design can include milestones or benchmarks for assessing data along the way. Researchers or IRBs might adjust the research design on the basis of data and information generated in the research thus far. In addition, they might reassess the risk-to-benefit ratio and consider halting the research if the potential risk is too great.

   d. Researchers can actively engage with communities that might be affected by the research, to discuss the potential benefits and risks of the research and to listen to stakeholders' concerns.

2. **What ethical considerations might arise when designing a study to test an experimental antimicrobial agent on bacteria? What ethical principles can be used to guide an assessment of such research?**

[67] *Protection of Human Subjects, HHS*, op cit; Jones, J.S., et al. (1996). Structure and practice of institutional review boards in the United States. *Academic Emergency Medicine*, 3(8), 804-809.

Starting points for discussion:

a. Public beneficence applies to research that does not involve human participants but still has broader implications for society. Researchers should design experiments to maximize the likelihood that results will advance scientific knowledge and public benefit. For example, researchers might choose to study the effects of an antimicrobial agent on a bacterial species that has potential for causing public harm.

b. Responsible stewardship calls for investigators to be mindful and attentive to risks as they design their research. As responsible stewards, researchers should adhere to professional ethics standards and establish processes for assessing likely benefits and risks of proposed research.

c. Democratic deliberation can guide an assessment of the research. Researchers can engage diverse input and participate in an open discussion and debate about the potential benefits, risks, and societal implications of the research.

3. What ethical considerations might arise when designing a randomized controlled trial (RCT) to test an experimental treatment to lower blood pressure? What ethical principles can be used to guide an assessment of such research?

Starting points for discussion:

a. Beneficence obligates researchers to act in a way that secures the wellbeing of research participants. Non-maleficence requires the researcher not to impose harm and to minimize harm that might occur to participants.

b. RCTs must take into consideration whether selecting a placebo design over an equivalence study design is acceptable when an effective intervention exists. In this case, several drugs for humans are approved for lowering blood pressure.

c. Obtaining informed consent from research participants demonstrates respect for persons. In the case of RCTs, ensuring that participants are fully informed about and understand the study design is essential, including the chance (through randomization) that they will not receive the experimental intervention.

d. Justice requires equitable participant and site selection to ensure a fair distribution of potential benefits and burdens of research. It requires that a project's research design not place undue burden on any specific group without compensating benefits.

e. Vulnerable populations might require additional protection to guard against potential exploitation in research conduct. In this case, participants who do not have access to medical care or prescription drugs might be considered a vulnerable population.

4. **Much of the language in the regulations and guidelines relevant to ethical research design emphasizes that proposed research must undergo independent review by someone other than the investigator (e.g. IRB, DSMB, DMC, or scientists not involved in the research) to assess its scientific rigor, relevance, and potential benefits and risks. Why is this impartial review important?**

   Starting points for discussion:

   a. Independent researchers can recognize flaws, limitations, or unnecessary risks in the proposed study design. They can examine assumptions about the quality of existing evidence that supports the research hypothesis and help spot conflicts that might not be obvious to the research team.

   b. Impartial reviewers assess a proposed research design from a fresh perspective. They might identify ethical considerations not previously recognized by the researchers, who can be entrenched in the particulars of a research design. The requirement for external review forces researchers to articulate and justify their study design in the early stages of research and encourages them to consider ethical questions early and explicitly in the research process.

   c. Impartial review can provide assurance that the study is based on acceptable scientific principles and reflects knowledge of the literature.

   d. Independent review for scientific merit can improve the study design, increasing the likelihood that the results will be meaningful.

VI. Exercises

Exercise A. *Just as placebo-controlled drug trials provide valuable information about the efficacy of experimental drugs, so too can placebo-controlled surgery trials provide valuable information about a surgery or medical procedure. Many patients with osteoarthritis in the knee report symptomatic relief after receiving a surgical procedure called arthroscopy. However, how the surgery achieves this relief is unclear. To determine whether the procedure is responsible for pain relief, researchers conducted a randomized, placebo-controlled trial.*

The following references provide useful information:

> Moseley, J.B., et al. (2002). A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *The New England Journal of Medicine*, 347(2), 81-88. Retrieved March 20, 2015 from http://www.ncbi.nlm.nih.gov/pubmed/?term=12110735. [Read the abstract only.]

Rogers, W., et al. (2014). Strengthening the ethical assessment of placebo-controlled surgical trials: Three proposals. *BMC Medical Ethics*, 15(78). Retrieved March 20, 2015 from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4223753/.

1. **What are the ethical concerns researchers must consider when designing a placebo surgery clinical trial for osteoarthritis of the knee? How might they differ from traditional placebo-controlled studies? How are they similar?**

2. **How might researchers address the ethical concerns of placebo surgery in their research design?**

Exercise B. *Poor research design in clinical trials can limit the potential relevance of research results. For example, some scholars argue that poor study designs are one reason that so few cancer treatments are approved by the FDA.*[68]

The following reference provides useful information:

Wapner, J. (2008, January 10). Group therapy: How poorly designed trials for cancer drugs are hurting patients. *Slate.* Retrieved March 20, 2015 from http://www.slate.com/articles/health_and_science/medical_examiner/2008/01/group_therapy.single.html.

1. **The article points out that cancer studies often do not directly compare two treatments in Phase 2 trials. How is this type of trial design ethically justified?**

2. **Consider the author's assertion that scientists might have other incentives when conducting research that could influence their research design. What are the ethical implications of these incentives?**

3. **Browse the National Cancer Institute's clinical trials registry (http://www.cancer.gov/clinicaltrials/search) and search for a Phase 2 clinical trial, then consider the following points.**

    a. Does the study design reflect a randomized controlled trial or a different structure? Why do you think the specific study design was chosen?

    b. Based on the information presented about the study design, might any considerations discussed in the cited *Slate* article be present in this particular study?

[68] Wapner, J. (2008, January 10). Group therapy: How poorly designed trials for cancer drugs are hurting patients. *Slate*. Retrieved March 20, 2015 from http://www.slate.com/articles/health_and_science/medical_examiner/2008/01/group_therapy.single.html.

c. What types of eligibility criteria are listed, and do any stand out in particular (e.g., minimum life expectancies, age, and sex) to you? Why or why not? What are the ethical implications of these criteria?

Exercise C: *The Office of Research Integrity blog provides a case study about peer review of research ("Getting a fair shake?").*

The following reference provides useful information:

Office of Research Integrity. (2014). Case study: Should you listen to a peer reviewer? [Webpage]. Retrieved March 20, 2015 from http://ori.hhs.gov/blog/case-study-should-you-listen-peer-reviewer.

1. **Based on this scenario, what are some of the merits and potential areas of concern in the peer review process?**

2. **Gail is considering resubmitting the proposal using the reviewers' suggested methods, but proceeding with her research as originally proposed (without modifying her actual protocol). What are the consequences of doing so?**

3. **Construct your own case study, reflecting ethical considerations investigators might encounter when designing their research.**

Exercise D. *Social networking sites have changed how individuals interact with each other. Some HIV/AIDS researchers are recruiting for research participation difficult-to-reach populations through social networking sites and online advertising organizations. Online recruitment raises some human subjects protections concerns. It also has called into question the validity and reliability of collected data.*

The following references provide useful information:

Protection of Human Subjects, HHS. 45 C.F.R. Part 46. Retrieved March 20, 2015 from http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html.

Curtis, B.L. (2014). Social networking and online recruiting for HIV research: Ethical challenges. *Journal of Empirical Research on Human Research Ethics*, 9(1), 58-70. Retrieved March 20, 2015 from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4316828/.

1. **How does the use of social networking sites and online advertising organizations for recruitment challenge the adequacy of participant protections provided through traditional informed consent, privacy, and confidentiality procedures? Do the current Common Rule regulations at 45 C.F.R. Part 46 provide sufficient guidance?**

2. **Construct your own additions to 45 C.F.R. Part 46 to ensure research participants recruited through the Internet are adequately protected.**

3. **Consider and outline how investigators might design research to ensure the validity and reliability of results obtained through Internet recruitment measures.**

VII. Glossary of Terms

Beneficence: An obligation on the part of researchers to undertake efforts to maximize possible benefits and minimize potential harms to research participants.

Common Rule: Current federal regulations that protect research participants, codified by the U.S. Department of Health and Human Services in the Code of Federal Regulations at 45 C.F.R. Part 46, Subpart A. Also known as "Human Subjects Regulations."

Community advisory board: An advisory board consisting of community members that represents the interests of the community in advising and communicating with researchers or research sponsors.

Community-based participatory research: Research in which the community helps to identify the topic or issue to be studied based on local priorities, actively participates in developing the study design, and provides guidance to the researchers regarding participant recruitment and retention.

Democratic deliberation: An approach to collective and collaborative decision making that seeks to clarify and articulate factual and ethical issues at the core of a debate, to create consensus whenever possible, and to map the terrain of disagreements in a respectful way—when agreement is not immediately attainable—by encouraging reciprocity, respect for persons, transparency, publicity, and accountability.

Equipoise: The state of uncertainty in the scientific and medical communities about whether an experimental drug or intervention is superior to a comparator (i.e., an established intervention or placebo).

Informed consent: The process of informing and obtaining permission from an individual before conducting medical or research procedures or tests.

Institutional review board (IRB): A specially constituted review body established or designated by an entity to protect the welfare of individuals recruited to participate in biomedical or behavioral research. The duties and responsibilities of IRBs are described in the federal regulations.

Justice: An ethical principle that calls for equitable distribution of benefits and burdens across society—for example, the benefits and burdens of biomedical research, or of technological advances. This principle is often referred to as distributive justice.

Non-maleficence: An obligation on the part of researchers not to cause intentional harm to research participants.

Protocol: A plan for the conduct of a research project, including all aspects of the project from recruitment to obtaining informed consent to dissemination of results.

Public beneficence: An ethical principle that encourages us to pursue and secure public benefits while minimizing personal and public harm.

Respect for persons: Ethical principle requiring that individuals are treated as independent and self-determining (autonomous) agents and that persons with diminished autonomy are entitled to additional protections.

Responsible stewardship: The act of ensuring and/or promoting consideration of the interests and needs of those not in a position to represent themselves in social discourse.

VIII. Additional Resources

Bailar, J.C. III. (2001). The powerful placebo and the Wizard of Oz. *New England Journal of Medicine*, 344(21), 1630-1632.

Berg, P., et al. (1975). Summary statement of the Asilomar conference on recombinant DNA molecules. *Proceedings of the National Academy of Sciences*, 72(6), 1981-1984.

Committee on Science, Engineering, and Public Policy; Institute of Medicine; Policy and Global Affairs; and National Academy of Sciences. (2009). *On Being a Scientist: A Guide to Responsible Conduct in Research*, Third Edition. Washington, DC: The National Academies Press. Retrieved March 20, 2015 from http://www.nap.edu/catalog/12192/on-being-a-scientist-a-guide-to-responsible-conduct-in.

Concato, J.S., Shah, N., and R. Horowitz. (2000). Randomized, controlled trials, observational studies, and the hierarchy of research designs. *New England Journal of Medicine*, 342(25), 1887-1892.

Freedman, B. (1987). Equipoise and the ethics of clinical research. *New England Journal of Medicine*, 317(3), 141-145.

Lilford, R.J. (2003). Ethics of clinical trials from a Bayesian and decision analytic perspective: Whose equipoise is it anyway? *BMJ*, 326(7396), 980-981.

Miller, F.G., and H. Brody. (2003). A critique of clinical equipoise. Therapeutic misconception in the ethics of clinical trials. *Hasting Center Report*, 33(3), 19-28.

Moreno, J.D. (1999). Ethics of research design. *Accountability in Research,* 7, 175-182.

National Bioethics Advisory Commission (NBAC). (2001). *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*. Bethesda, MD: NBAC.

Shapiro, H.T., and E.M. Meslin. (2001). Ethical issues in the design and conduct of clinical trials in developing countries. *New England Journal of Medicine*, 345(2), 139-142.